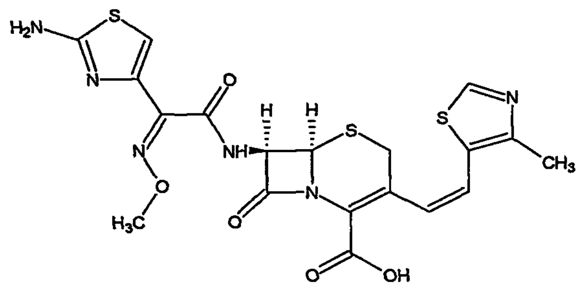
PROCESS FOR SELECTIVE PREPARATION OF Z-ISOMER OF CEFDITOREN AND PHARMACEUTICALLY ACCEPTABLE SALTS AND ESTERS THEREOF

Field of the Invention

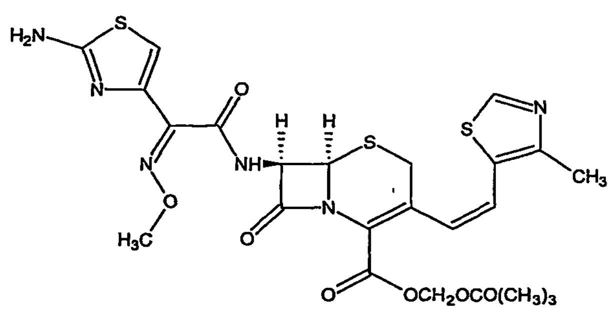
The present invention relates to a process for selective preparation of Z-isomer of cefditoren of Formula I and pharmaceutically acceptable salts and esters thereof. Cefditoren possesses a wide spectrum of antibacterial activity against Gram-positive and Gram-negative bacteria.



FORMULA I

Background of the Invention

[6R-[3(Z),6a,7b(Z)]]-7-[[(2-Amino-4-thiazolyl)(methoxyimino)acetyl]amino]-3-[2-(4-methyl-5-thiazolyl)ethenyl]-8-oxo-5-thia-1-azabicyclo[4.2.0]oct-2-ene-carboxylic acid, pivaloyloxy methyl ester of Formula Ia, which is known as cefditoren pivoxil, is a third generation cephalosporin developed with an aim of producing active cephalosporins with potent and broad-spectrum activity (European Patent No. 175610). Cefditoren pivoxil is highly active not only against a variety of gram-positive and gram-negative bacteria but also against some resistant strains of bacteria.



FORMULA Ia

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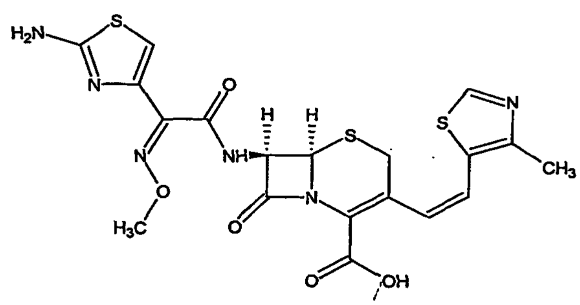
European Patent No. 175610 describes a process for preparation of cefditoren and its pharmaceutically acceptable salts and esters. The process described is non-selective and gives more than 20% of unwanted E-isomer, which is then separated by means of column chromatography. The yield of cefditoren or its sodium salt or its pivaloxymethyl ester is reported to be very low.

U.S. Patent No. 6,288,223 describes a process for the selective preparation of the Z-isomer of 3-2 (substituted vinyl)cephalosporins. The process described uses stringent conditions for deprotection of the protected amino and carboxyl functionalities. The process isolates every intermediate followed by its purification and therefore is very time consuming and expensive. It gives a low yield of cefditoren pivoxil.

U.S. Patent No. 5,616,703 describes a process for separation of cephalosporin isomers by forming amine salts. The process described therein produces the intermediates in which the unwanted E isomer is more than 20%, which is then depleted by forming amine salts. In this process the yield of the intermediate is diminished and the unwanted E-isomer discarded after separation.

Summary of the Invention

Herein is provided a cost-effective and selective process for the preparation of cefditoren of Formula I and salts and esters thereof, wherein the desired Z-isomer of the cefditoren and salts and esters thereof are obtained without involving the purification of either the intermediates or the final product for removing the E-isomer.

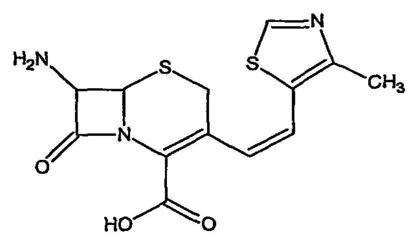


FORMULA I

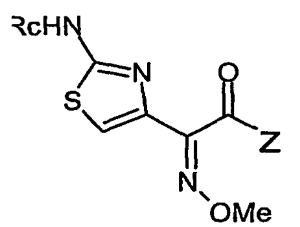
Further, herein are provided reaction conditions for formation of cefditoren pivoxil wherein less than 2% of the E-isomer is formed during the reaction.

Further, herein is provided a process including an enzymatic deacylation of the aminoacyl group present on the 7-position of the cephalosporin nucleus in approximately neutral to slightly alkaline conditions wherein the hydrolysis of the β-lactam ring is strongly inhibited or prevented resulting into higher yield of the product having fewer impurities.

Further, herein is provided a process for the selective preparation of cefditoren of Formula I and salts and esters thereof, wherein 7-amino-3-[(4-methylthiazol-5-yl)vinyl]-3-cephem-4-carboxylic acid (hereinafter referred to as 7-ATCA) of Formula IX is treated with activated esters of 2-methoxyimino-2-(2-aminothiazole-4-yl)acetic acid of Formula X.

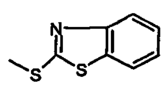


FORMULA IX

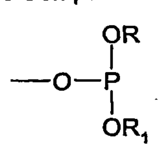


Formula X

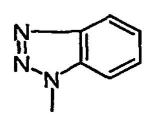
wherein Z is Compound of Formula Xa or Xb or Xc or Xd



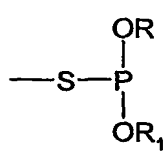
Formula Xa



Formula Xb



Formula Xc

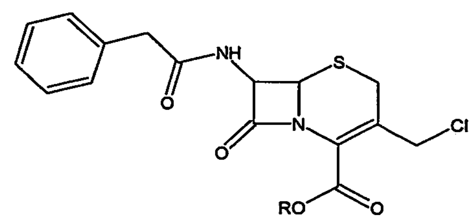


Formula Xd

Further, herein is provided Z-enriched 7-ATCA of Formula IX having less than 2% of unwanted E-isomer obtained without carrying out purification steps.

Further, herein is provided crystalline hydrates of sodium and potassium salts of cefditoren having specific XRD pattern, exemplified in Figure 1 and Figure 2.

Further, herein is provided a process for preparation of 7-ATCA of Formula IX from 7-phenylacetamido-3-chloromethyl-3-cephem-4-carboxylate (hereinafter referred to as PCMCC esters) of Formula II wherein the process can be carried out in single reaction vessel without the need to isolate any intermediate.



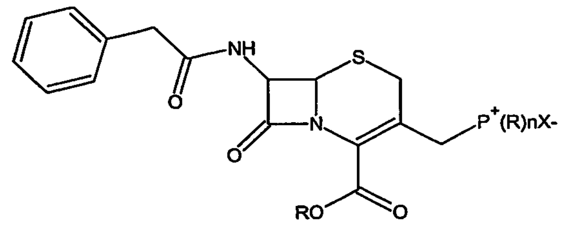
FORMULA II

Further, herein is provided a cost-effective and simple three-step process for conversion of esters of 7-phenylacetamido-3-chloromethyl-3-cephem-4-carboxylate (hereinafter referred to as PCMCC esters) of Formula II to cefditoren pivoxil of Formula Ia which would otherwise require eight steps.

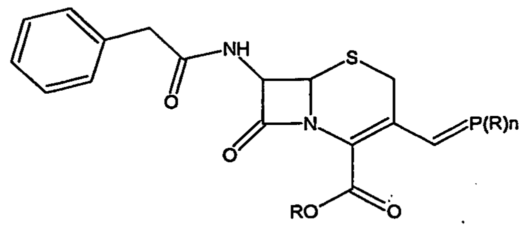
Detailed Description of the Invention

In one aspect, herein is described a process for preparation of cefditoren of Formula I or salts and esters thereof from PCMCC esters of Formula II in three steps.

In a first step, esters of PCMCC of Formula II such as p-methoxybenzyl ester (hereinafter referred to as GCLE) or diphenylmethyl ester are treated with an alkali or alkaline earth metal halide, such as an iodide or bromide, and a phosphorous-containing compound of Formula III which is $P(YR)_n$, wherein Y is absent or oxygen or sulphur, n is an integer 2, 3 or 4 and R can be C_1 to C_7 straight or branched chain alkyl, alkenyl, alkynyl or C_6 to C_{10} aryl or aralkyl in an organic solvent to get intermediate phosphonium salt of Formula IV, which is reacted *in-situ* with an organic or inorganic base to get an ylide of Formula V.

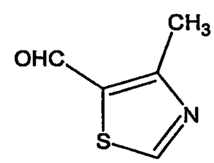


FORMULA IV

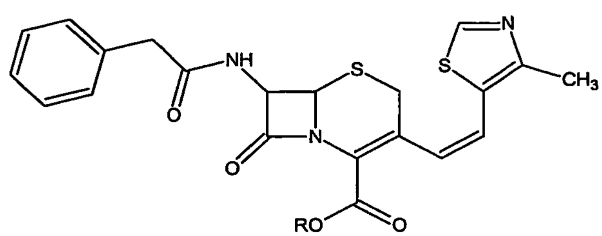


FORMULA V

The ylide was treated *in-situ* with 4-methylthiazole-5-carboxaldehyde of Formula VI to get ester of 7-acetamido-3-[(4-methylthiazol-5-yl)vinyl]-3-cephem-4-carboxylate of Formula VII (herein onwards referred to as DPTC).

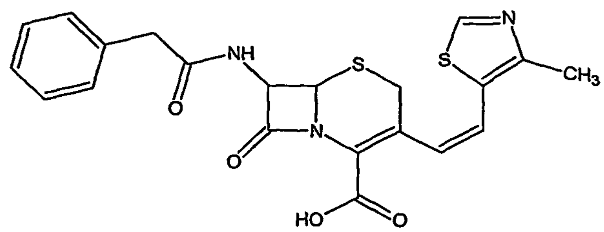


FORMULA VI



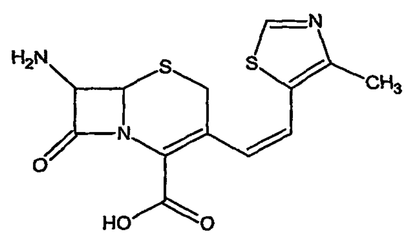
FORMULA VII

Deprotection of the carboxylic group using a phenol or its ether gave 7-acetamido-3-[(4-methylthiazol-5-yl)vinyl]-3-cephem-4carboxylic acid of Formula VIII (herein onwards referred to as MPTC).



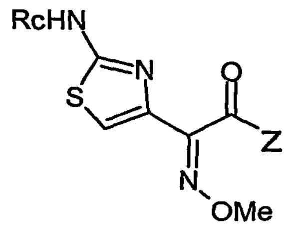
FORMULA VIII

MPTC is subjected to enzymatic deacylation reaction at a pH of from about 5 to about 8 to get an intermediate 7-ATCA of Formula IX which is isolated as white crystalline solid having less than 2% of E-isomer, without carrying out purification steps. The typical overall yield from GCLE to 7-ATCA is, for example, 55%. The reaction sequence from GCLE to 7-ATCA can be carried out without isolating / purifying any intermediate compounds. However, the isolation and purification of every intermediate was also carried out to establish purity and impurity profiles.



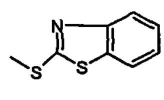
FORMULA IX

In a second step, 7-ATCA is treated with optionally 2-amino protected, activated esters of 2-methoxyimino-2-(2-aminothiazole-4-yl)acetic acid of Formula X, wherein Z can be substituents of Formula Xa, Xb, Xc, Xd and R_c is monovalent or divalent amino protecting group such as trityl (triphenylmethyl), acetyl, benzhydryl or acetamidophenyl, R can be C_1 to C_7 straight or branched chain alkyl, alkenyl, alkynyl or C_6 to C_{10} aryl or aralkyl; R_1 is C_{1-6} straight or branched chain alkyl, cycloalkyl, aryl, aralkyl or a heterocycle residue, in the presence of an organic solvent and a base to get cefditoren acid, which can be converted to its sodium salt of Formula Ib. The sodium salt is isolated as crystals, wherein the unwanted E-isomer is less than 1%.

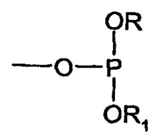


Formula X

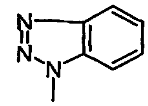
wherein Z is Compound of Formula Xa or Xb or Xc or Xd



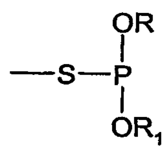
Formula Xa



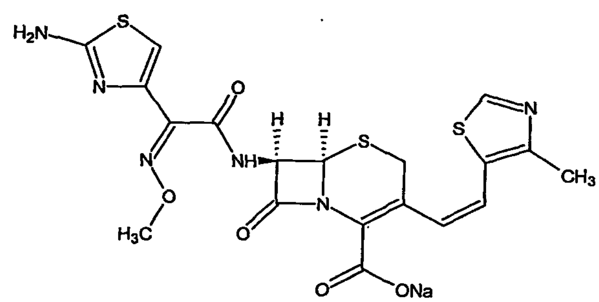
Formula Xb



Formula Xc

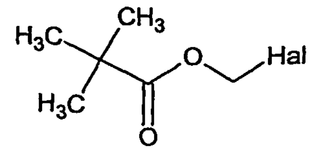


Formula Xd

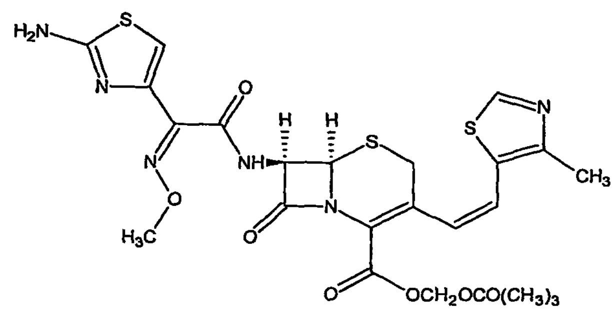


FORMULA Ib

In a third step, the sodium salt of cefditoren acid is treated with halomethyl pivalate of Formula XI, wherein the halo group is bromo or iodo, in an organic solvent to get pharmaceutically acceptable ester of cefditoren of Formula Ia, which can be optionally purified to get a desired pharmacopoeial purity.



FORMULA XI



FORMULA Ia

The first step of preparation of 7-ATCA having less than 1% of unwanted E-isomer includes five operations (i) through (v), which are carried out *in-situ* without isolating any intermediate.

In (i), PCMCC ester of Formula II is treated with alkali or alkaline earth metal halide, such as iodide or bromide, and a phosphorous-containing compound of Formula III in organic solvent optionally containing water, at a temperature of about -10 to about 50°C. The molar ratio of alkali or alkaline earth metal halide and compound of Formula III used can be selected in the range of from about 0.98 to about 1.25 per mole of Formula II.

Alkali or alkaline earth metal iodide or bromide can be selected from sodium iodide, potassium iodide, sodium bromide, potassium bromide and such similar metal iodides or bromides.

The compound of Formula III wherein Y is absent or oxygen or sulphur, n is an integer 2, 3 or 4 and R is selected from C_1 to C_7 straight or branch chain alkyl, alkenyl, alkynyl or C_6 to C_{10} cycloalkyl, aryl or aralkyl can be, for example, trimethylphosphine, triethylphosphine, tributylphosphine, triphenylphosphine, triethylphosphite, triphenylphosphite, triethylorthophosphite or triphenylorthophosphite.

The organic solvent can be selected from, for example, chlorinated hydrocarbons such as methylene chloride, chloroform, ethylene chloride or ethylene bromide; ethers such as tetrahydrofuran, diisopropyl ether, 1,4-dioxane or diethyl ether; ketones such as acetone, methyl isobutyl ketone, methyl ethyl ketone; and lower alcohols such as methanol, ethanol, propanol, isopropanol, butanol or mixtures thereof.

The presence of water in the reaction can assist the dissolution of metal halide, and can also make the reaction mixture biphasic, so that the inorganic as well as organic side products formed are dissolved and do not actually interfere in the reaction. The quantity of water to be used in the reaction can vary according to the reaction temperature or moles of reactants and can be from about 1:0.5 to about 1:2 with respect to the quantity of organic solvent.

The temperature of the reaction can be between about -5 to about 50°C. After completion of the reaction, layers can be separated and the organic layer can be used as such for (ii). It is also possible to concentrate the organic layer under vacuum and isolate the product optionally under strict anhydrous conditions.

In (ii) the organic layer obtained in (i) (or the product isolated after concentration of the organic layer) is treated with a base at a temperature between about -20 to about 50°C. It is also possible that the organic layer obtained in a) i) is cooled to about -5 to about 10°C and a solution of base in water or an organic solvent is added slowly over a period of 15 minutes to 1 hour while maintaining the temperature. A solution of base can be made in a suitable solvent such as water. The strength of such alkali solution can be, for example, 0.2 to 1.2 M. The reaction mass after addition of the base is further stirred for about 20 minutes to about 1 hour at about -5 to about 10°C in order to promote completion of the reaction.

The base used in this step can be an inorganic compound such as sodium hydroxide, potassium hydroxide, calcium hydroxide, magnesium hydroxide, aluminium hydroxide, sodium hydride, potassium hydride, sodium carbonate, potassium carbonate, sodium bicarbonate, potassium bicarbonate or organic salts such as sodium methoxide, potassium t-butoxide, sodium ethoxide, or organic ammonium compounds such as triethylamine, dicyclohexylamine or diphenylamine.

Upon completion of reaction, the organic layer can be separated from the aqueous layer and dried over anhydrous sodium sulphate, magnesium sulphate or a suitable drying agent known to a person skilled in the art. After adjusting the volume of the organic layer with solvent used earlier, it can be used as such in (iii).

In (iii), to the organic layer obtained in (ii) which contains a solution of ylide of Formula V in chlorinated hydrocarbons such as chloroform or methylene chloride is added another organic solvent which can be a lower alkanol such as methanol, ethanol, n-propanol, isopropanol and n-butanol; an ether such as tetrahydrofuran, diethyl ether, 1,4-dioxane; an ester such as ethyl acetate, n-butyl acetate, isopropyl acetate etc or a ketone such as acetone, ethyl methyl ketone etc. or mixtures thereof. In some embodiments, a lower alkanol is used. The ratio of chlorinated hydrocarbon to lower alkanol can vary from about 1:1 to about 1:0.25.

The above reaction mass containing a mixture of solvents in the mentioned ratio-containing product of step (ii) is cooled to about -50 to about -5°C and to it added 4-methylthiazole-5-carboxaldehyde of Formula VI. The reaction mixture is stirred for 15 to 35 hours at about –50 to about 30°C. Upon completion of the reaction, it is quenched by addition of water, followed by washing of the organic layer with sodium bisulphite solution to reduce aldehydic and related impurities generated during the reaction. The organic layer is concentrated under reduced pressure to get a brown-coloured residue of DPTC of Formula VII, which can be used as such in the next step without any purification or isolation.

In (iv), DPTC of Formula VII is treated with a phenol or its ether for deprotection of the carboxyl-protecting group at a temperature of about 0 to about 100°C. The reaction can be carried out in presence of an organic solvent such as lower alkanol, chlorinated hydrocarbon or acetone. However, the reaction can be carried out without using any solvent.

A phenol or its ether can be, for example, anisole, 2-cresol, 3-cresol, 4-cresol, resorcinol, catechol, 2-mercaptophenol, 3-mercaptophenol, and 2-methoxyphenol. When anisole is used for deprotection of the carboxyl-protecting group, an acid catalyst which can be selected from a group comprising trifluoroacetic acid, formic acid or Lewis acids such as aluminium chloride, boron trifluoride, and anhydrous zinc chloride can be used. Upon completion of the reaction, n-butyl acetate can be added to the reaction mixture and

the organic layer can be extracted with sodium bicarbonate solution. The sodium salt of the product is extracted in the aqueous layer, which after separating the layers is washed with n-butyl acetate to remove traces of deprotecting agent. The aqueous layer obtained above can be used as such in the next operation without isolating the product, MPTC of Formula VIII.

Deprotection of an amino group is a well-known art in the field of, for example, production and purification of penicillins and cephalosporins. Deprotection mostly involves deacylation, for which several processes are available (European Patent No. 175610, PCT patent application WO 02/18618, US patent application 20020006642 and US patent application 20020058302). In context to (v), deacylation of the 7-amino group of the β-lactam ring can employ milder reaction conditions, which are not deleterious to the β-lactam nucleus.

When enzymatic deacylation of sodium salt of MPTC of Formula VIII is carried out under pH of about 5 to about 8 and at a temperature from about 0 to about 50°C, hydrolysis of the β-lactam ring is negligible, and the yield of desired product 7-ATCA of Formula IX is almost quantitative.

The reaction can be carried out in water optionally containing an organic solvent, which can be miscible or immiscible with water. Such solvent can be selected from lower alkanols such as methanol, ethanol and isopropanol; esters such as ethyl acetate, n-butyl acetate, isopropyl acetate; ethers such as tetrahydrofuran, diethyl ether; chlorinated hydrocarbons such as chloroform, methylene chloride, ethylene chloride and ketones such as acetone.

Enzymes suitable for deacylation reactions are, for example, known as penicillin acylases or penicillin amidases. These enzymes are classified as E.C. 3.5.1.11. Such enzymes, for example Penicillin G amidase, may be isolated from, for example, microorganisms such as fungi and bacteria. The enzyme can be used in immobilized form, which can be suitably kept wet to maintain the activity of the enzyme intact.

The pH of the reaction mass can be kept in the range of about 5 to about 8. During this reaction, after deacylation of 7-phenylacetamido group of MPTC, phenyl acetic acid is formed as a by-product which decreases the pH of the reaction mass. In order to maintain the pH, a base can be added intermittently to the reaction mass. Such a base can be, for example, sodium carbonate, sodium bicarbonate, sodium hydroxide, potassium hydroxide,

potassium bicarbonate, potassium carbonate or water soluble ammonium compounds such as ammonium hydroxide or triethylamine.

The reaction temperature can be kept between about 0 to about 50°C. Upon completion of the reaction, the enzyme can be filtered and the resultant aqueous filtrate can be acidified with suitable mineral acid such as hydrochloric acid to pH of from about 3 to about 3.5 to affect precipitation of 7-ATCA of Formula IX at its iso-electric point. Such obtained 7-ATCA of Formula IX contains about 95% or more of the desired Z-isomer, having less than 2% of the undesired E-isomer impurity.

The intermediate compound 7-ATCA of Formula IX is obtained in good yield and in excellent purity. The content of E-isomer impurity in 7-ATCA of Formula IX according to processes described herein can be less than 1%. 7-ATCA of Formula IX is a useful intermediate in the synthesis of several cephalosporins. The process for the preparation of 7-ATCA can be employed in the synthesis of several cephalosporins other than cefditoren or pharmaceutically acceptable salts and esters thereof.

In a second step, 7-ATCA is treated with activated esters of 2-methoxyimino-2-(2-optionally protected aminothiazole-4-yl)acetic acid of Formula X, wherein Z can be a substituent of Formula Xa, Xb, Xc, Xd and R_c is monovalent or divalent amino protecting group selected from, for example, trityl (triphenylmethyl), acetyl, benzhydryl or acetamidophenyl, in the presence of an organic solvent, optionally containing water, and using a base at a temperature of about -20 to about 60°C to get cefditoren of Formula I.

The activated ester of 2-methoxyimino-2-(2-optionally protected aminothiazole-4-yl)acetic acid of Formula X can be, for example, 2-methoxyimino-2-(2-amino thiazol-4-yl)acetic acid, benzotriazol-1-yl ester; 2-methoxyimino-2-(2-amino thiazol-4-yl)acetic acid, S-2-benzothiazole ester (herein onwards referred as MAEM); 2-methoxyimino-2-(2-amino thiazol-4-yl)acetic acid, dialkylphonate ester or diarylphosphonate ester; 2-methoxyimino-2-(2-amino thiazol-4-yl)acetic acid, dialkylphosphothionate ester or diarylphosphothionate ester.

The solvent for this reaction can be, for example, chlorinated hydrocarbon such as methylene chloride, chloroform, ethylene chloride or ethylene bromide; ethers such as tetrahydrofuran and diethyl ether; ketones such as acetone, methyl isobutyl ketone and methyl ethyl ketone; alcohols such as methanol, ethanol, propanol, isopropanol and butanol or mixtures thereof optionally containing water.

The base used in this step can be an inorganic compound such as sodium hydroxide, potassium hydroxide, calcium hydroxide, magnesium hydroxide, aluminium hydroxide, sodium hydride, potassium hydride, sodium carbonate, potassium carbonate, sodium bicarbonate, potassium bicarbonate or organic salts such as sodium methoxide, potassium t-butoxide, sodium ethoxide, or organic ammonium compounds such as triethylamine, dicyclohexylamine or diphenylamine.

For the purpose of the reaction, the base can be added slowly after preparing a solution of 7-ATCA and MAEM in a mixture of solvents. The reaction can be carried out at a temperature of about -20 to about 60°C. Upon completion of the reaction, dichloromethane can be added to quench the reaction and the layers can be separated. The aqueous layer can be acidified to adjust the pH between about 4.5 to about 5. Cefditoren acid of Formula I can precipitate, and which can be filtered and purified using a solvent or by column chromatography.

Alternatively, to the aqueous layer as obtained above can be added acetone and sodium 2-ethylhexanoate at a temperature of about 15 to about 30°C to produce a sodium salt of cefditoren. The sodium salt can precipitate from the reaction mass as crystalline solid. To further the crystallization, acetone can be optionally added to the reaction mass and the product can be filtered.

The sodium salt of cefditoren thus obtained can have an HPLC purity above 98% wherein the E-isomer as determined by HPLC can be less than or equal to 1%. The crystalline sodium salt can have up to about 6.5 to about 7% moisture, which suggests that it could be a novel dihydrate of the cefditoren sodium.

In a similar manner using potassium acetate instead of sodium 2-ethylhexanoate, a potassium salt of cefditoren can be prepared from cefditoren acid. The potassium salt can contain up to about 6 to about 7% intrinsic moisture, which suggests that it is in dihydrate form.

The salts of cefditoren acid such as calcium, magnesium, zinc, copper, nickel, manganese, rubidium, cobalt, strontium and the like can be prepared using appropriate salt-forming agents known to a person skilled in the art.

These crystalline forms of cefditoren salts can be very good candidates for development of parenteral dosage forms of cefditoren owing to their high solubilities and stabilities in aqueous conditions.

In a third step, the sodium or potassium salt of cefditoren or cefditoren acid can be dissolved in an organic solvent and reacted with halomethyl pivalate of Formula XI wherein the halo group is chloro or bromo or iodo, at a temperature of about -25 to about 35°C. Upon completion of the reaction, cefditoren pivoxil is obtained by a suitable aqueous work-up followed by extraction with organic solvent. Any organic solvent may be used for extraction which is known to a person of ordinary skill in the art. The solution of cefditoren pivoxil in organic solvent is partially concentrated by evaporation of solvent under vacuum. The product can be then precipitated from the concentrated solution by addition of an anti-solvent selected from, for example, n-hexane, diethyl ether, diisopropyl ether, cyclohexane and cycloheptane. The precipitated product is then filtered and can be purified by further crystallization or by column chromatography using hexane-ethyl acetate as eluent.

The compound of Formula XI can be selected from, for example, iodomethyl pivalate, bromomethyl pivalate, chloromethyl pivalate.

The organic solvents can be selected from, for example, dimethylformamide, dimethylacetamide, dimethylsulphoxide, tetrahydrofuran, 1,4-dioxane.

While the present invention has been described in terms of its specific embodiments, certain modifications and equivalents will be apparent to those skilled in the art and are intended to be included within the scope of the present invention.

Example 1: Preparation of 7-ATCA

To a stirred mixture of 4-methoxybenzyl 3-(chloromethyl)-8-oxo-7-[(phenylacetyl)amino]-5-thia-1-azabicyclo[4.2.0]oct-2-ene-2-carboxylate (10 g, 20.5 mmol) in 60 ml of water and 60 ml of chloroform, was added sodium iodide (3.23 g, 21.5 mmol) and triphenyl phosphine (5.65 g, 21.5 mmol). The heterogeneous mixture was stirred at 25 – 30°C for 3 hrs. The bottom organic layer was separated and cooled to 0 – 5°C. To this a solution of sodium hydroxide (50 ml, 0.4M) was added at 0–5°C in 20–30 minutes, followed by agitation of 30 minutes at the same temperature. The bottom organic layer was separated and dried over anhydrous sodium sulphate. The volume of the organic layer was adjusted to 120 ml by chloroform. Organic layer containing ylide was cooled to –10 to –15°C and n-propanol (40 ml) was added, followed by addition of 4-methylthiazole-5-carboxaldehyde (8.0 g, 62.9 mmol). Reaction mixture was stirred for 20–24 hours at –10 to –15°C after end of which it was quenched by addition of water (100 ml)

followed by washing of organic layer with sodium bisulfite solution. Organic layer was concentrated under reduced pressure to get a brown coloured residue. Phenol (50 ml) was added to the residue to get a clear solution. This solution was stirred at 40–50°C for 10–12 hours and n-butyl acetate (100 ml) was added to the reaction mass followed by cooling to 5–10°C. Organic portion was extracted with sodium bicarbonate solution (0.17 Molar, 2 x 100 ml). Aqueous layer was washed with n-butyl acetate (2 x 100 ml) to remove traces of phenol. To clear aqueous layer was added Pen-G amidase (5 g wet) at 20–25°C. The pH of reaction was intermittently adjusted to 7.5 to 7.7 by slow addition of 5% sodium carbonate solution. After completion of reaction, enzyme was filtered and washed with de-ionized water. The filtrate was treated with activated carbon and then filtered at 30–35°C. Filtrate was cooled to 20–25°C and to it added dilute HCl (2 Molar) to adjust the pH to 3.0 to 3.5 in order to affect complete precipitation of 7-ATCA. Product was filtered and sequentially washed with water and acetone and finally dried under vacuum to get 3.5 g of off-white title compound in overall yield of 52%.

Purity (% Area, by HPLC): 96.3%
E-isomer impurity (% Area, by HPLC): 1.87%
^{1}H-NMR (300 MHz, DMSO-d_6): 2.36 (s, 3H); 3.1 – 3.5 (m, 2H merged with DMSO-peak); 4.81 – 4.83 (d, 1H); 5.05 – 5.07 (d, 1H); 6.31 – 6.35 (d, 1H); 6.65 – 6.69 (d, 1H); 8.91 (s, 1H).

Example 2A: Preparation of Cefditoren Sodium

A suspension of 7-ATCA of Formula IX (5.0 g, 15.4 mmol) and *S*-(1,3-benzothiazol-2-yl)-(2-amino-1,3-thiazol-4-yl)(methoxyimino)ethanethioate (6.7 g, 18.6 mmol) in aqueous THF (60 ml) was stirred at 0 – 5°C. Triethylamine (2.3 ml) was added slowly at 0–5°C over 15–20 minutes. The mixture was stirred at 0–5°C for 2–3 hours. Reaction was quenched by addition of dichloromethane followed by layer separation. Aqueous layer was diluted with acetone to 50 ml. Sodium 2-ethylhexanoate (3.3 g, 19.8 mmol) was added to aqueous acetone solution at 20–25°C. After stirring the mixture for sufficient time for crystallization of sodium salt of cefditoren, added acetone (50 ml) slowly to the reaction mass in order to complete crystallization. Filtered the crystallized product under suction and washed with acetone (2 x 10 ml). Product was vacuum dried to get 6.5 g of off-white title compound in 75% yield.

Water (Intrinsic water as measured by TGA): 6.9%

HPLC Purity: 98%

Z/E ratio (% Area, by HPLC): 99:1

^{1}H-NMR (300 MHz, D_2O): 2.42 (s, 3H); 3.45 (dd, 2H); 4.04 (s, 3H); 5.40 (d, 1H); 5.89 (d, 1H); 6.34 (d, 1H); 6.67 (d, 1H); 7.04 (s, 1H); 8.81 (s, 1H).

Example 2B: Preparation of Cefditoren Potassium

A suspension of 7-ATCA (1.0 g, 3.09 mmol) and *S*-(1,3-benzothiazol-2-yl)-(2-amino-1,3-thiazol-4-yl)(methoxyimino)ethanethioate (1.34 g, 3.82 mmol) in aqueous tetrahydrofuran (12 ml) was stirred at 0 – 5°C. Triethylamine (0.34 g) in THF (1.0 ml) was added slowly at 0 – 5°C over 15 – 20 min. The mixture was stirred at 0 – 5°C for 2 – 3 hrs. Reaction was quenched by addition of dichloromethane followed by layer separation. Aqueous layer was diluted by acetone to 10 ml. Potassium acetate (0.36 g, 3.67 mmol) was added to aqueous acetone solution at 20 – 25°C. Stirred the reaction mixture for sufficient time to affect crystallization of potassium salt. Added acetone (50 ml) slowly to the reaction mass to complete crystallization. Filtered under suction and washed with acetone (5 ml). Product was vacuum dried to get 1.5 g of off-white product (Yield = 89%).

Water (Intrinsic water as measured by TGA): 6.54%

HPLC Purity: 98.1%

Z/E ratio (% Area, by HPLC): 99:1

^{1}H-NMR (300 MHz, D_2O): 2.40 (s, 3H); 3.3 – 3.6 (m, 2H); 4.08 (s, 3H); 5.4 (d, 1H); 5.8 (d, 1H), 6.30 (d, 1H); 6.71 (d, 1H); 7.0 (s, 1H); 8.8 (s, 1H)

Example 3: Preparation of Cefditoren Pivoxil

To a stirred mixture of cefditoren sodium (20 g) in dimethylformamide (120 ml) at –15°C, iodomethyl pivalate (10 g) was added in one lot. Reaction mixture was stirred at –10 to –15°C for 60 min. Subsequently it was quenched by pouring reaction mixture in de-ionized water and ethyl acetate. Ethyl acetate layer was washed sequentially by water, 0.5% $NaHCO_3$ and 0.1% HCl and finally by water. Organic layer was dried over anhydrous sodium sulfate and concentrated under reduced pressure till residual volume is about 120 ml.

This solution was slowly added to n-hexane (700 ml) at ambient temperature and stir 30 min. The product was filtered under suction and dried under vacuum to get 18.4 g cefditoren pivoxil.

Yield: 78%

HPLC Purity: 96.8%

E-isomer of cefditoren pivoxil: 0.78%